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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/738,540 | 12/14/2000 | Wyne Pun Lee | P1795R1 | 2012 |

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GENENTECH, INC.
1 DNA WAY
SOUTH SAN FRANCISCO, CA 94080

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| EXAMINER |
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HADDAD, MAHER M

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| ART UNIT | PAPER NUMBER |
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1644

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DATE MAILED: 02/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/738,540

Applicant(s)

LEE ET AL.

Examiner

Maheer M. Haddad

Art Unit

1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 22 January 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,6-9 and 18-25 is/are pending in the application.
- 4a) Of the above claim(s) 21-23 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,6-9,18-20,24 and 25 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) <u>4</u> . | 6) <input type="checkbox"/> Other: |

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 1/22/03 (Paper No. 10), is acknowledged.

Claims 1, 6-9 and 18-25 are pending.

2. Newly submitted claims 21-23 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: the newly claimed anti-TNF α antibody does not share substantially structure common to the originally claimed immunoadhesion TNF α .

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 21-23 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

3. Claims 1, 6-9, 18-20 and 24-25 are under consideration in the instant application as they read on a method of treating rheumatoid arthritis, comprising administering to mammal in need thereof effective amounts of an anti CD11a antibody and a TNF- α antagonist, wherein the TNF- α antagonist is TNF- α receptor-IgG Fc fusion protein.

4. Claims 21-23 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention.

5. Applicant's IDS, filed 07-2-01 (Paper No. 4), is acknowledged. Examiner was able to locate the missing documents, therefore the PTO-1449 is initialed, signed and dated.

6. In view of the amendment filed on 1/22/03, paper No. 10, only the rejections set forth below.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1, 6-8 and 19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating rheumatoid arthritis, comprising administering to a mammal in need thereof effective amounts of an anti-CD11a antibody and a TNF- α -receptor-IgG Fc fusion protein, does not reasonably provide enablement for a method of treating rheumatoid arthritis, comprising administering an anti-CD11a antibody and any TNF- α antagonist in claim 1, wherein the anti-CD11a antibody is a non-T cell

Art Unit: 1644

and any TNF- α antagonist in claim 1, wherein the anti-CD11a antibody is a non-T cell depleting in claim 6, wherein the TNF- α antagonist is any immunoadhesion in claim 7, wherein the immunoadhesion is a fusion of at least a TNF- α binding portion of a TNF- α receptor and an immunoglobulin constant domain sequence in claim 8. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims essentially for the same reasons set forth in the previous Office Action, paper No. 8, mailed 7/16/02.

9. Claims 1, 6-8 and 19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention essentially for the same reasons set forth in the previous Office Action, paper No. 8, mailed 7/16/02.

Applicant is in possession of a method of treating rheumatoid arthritis, comprising administering to a mammal in need thereof effective amounts of an anti-CD11a antibody and a TNF- α -receptor-IgG Fc fusion protein.

Applicant's arguments, filed 1/22/03 (Paper No. 10), have been fully considered, but have not been found convincing.

Applicants argue that the specification on pages 3 and 16-17 discloses numerous examples of TNF- α antagonists. Applicants further argue that the specification fully provides guidance on how to make LFA-1 and TNF- α antagonists and how to use these molecules to treat rheumatoid arthritis and other disorders mediated by LFA-1 and TNF- α .

However, the claims as written encompass a broad genus of TNF α antagonists with an unlimited number of possibilities with regard to the length of the TNF α -binding portion of TNF α receptor. Further, the enablement issues of making the immunoadhesion still remain because the specification does not teach and provide sufficient guidance as to which amino acid of TNF α would have been altered such that the resultant TNF α portion would have retained the function to transduce cytotoxic and proliferative signals. The specification fails to provide any guidance on how to any TNF- α antagonist, any TNF- α binding portion, or any immunoadhesin that can be used to treat rheumatoid arthritis in mammal.

There is insufficient guidance as to which amino acid portions within the receptor can be unique and retain a distinct functional capability of TNF- α receptor polypeptide. Ngo *et al* teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure will require guidance (see Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). *In re Fisher*, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary

Art Unit: 1644

in order to satisfy the statute. Since the amino acid sequence of a polypeptide determined its structural property, predictability of which amino acid portion can retain the functional capabilities of the TNF- α receptor requires knowledge of, and guidance with regard to, which portions in the polypeptide contribute to its function.

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 1, 6-9, 18-20 and 24-25 are rejected under 35 U.S.C. 103(a) as being obvious over U.S. Patent No. 6,037,454, in view of U.S. Patent No. 6,306,820 or in view of the known fact disclosed in the specification on page 16, line 5 and page 17, lines 4-5.

The '454 patent teaches humanized anti-CD11a antibodies that can be administered to mammal at the same time or at separate times from the CD11 antibody with an immunosuppressive agent to treat LFA-1 mediated disorder such as rheumatoid arthritis (column 4 lines 35-67 and column 5, lines 1-37 in particular). The '454 patent further teaches that the LFA-1 antibody need not be, but is optionally formulated with one or more agents currently used to prevent or treat the disorder in question (column 31, lines 24-27 in particular).

The claimed invention differs from the reference teachings only by the recitation of TNF- α antagonist in claim 1, the TNF- α antagonist is an immunoadhesin in claim 7, the immunoadhesin is a fusion of at least a TNF- α binding portion of a TNF- α receptor and an immunoglobulin constant domain sequence in claim 8, wherein the immunoadhesin is a TNF- α -receptor-IgG Fc fusion protein in claim 9, the fusion protein consists of the extracellular ligand binding portion of human tumor necrosis factor receptor linked to the hinge, CH2 and CH3 domains of human IgG1 in claim 18 and the method of treating an LFA-1 or a TNF- α mediated disorder, further comprising administering to the mammal an effective amount of methotrexate in claim 19.

The '820 patent teaches the ability of TNFbp product(s) (e.g., sTNFR-I, sTNFR-II, sTNFR fragments (2.6 D sTNFRs such as 2.6 D sTNFR-I) or sTNFR Fc(s) (sTNFR-I/IgG1 or sTNFR-II/IgG1) and methotrexate to act synergistically in the treatment of various symptoms associated with TNF-mediated diseases, including acute and chronic inflammation such as rheumatic

Art Unit: 1644

diseases. The '820 patent further teaches the amino-terminal or carboxy-terminal fusion of a TNFbp(s) with all or part of the constant domain of the heavy or light chain of human immunoglobulin (individually or collectively, ("sTNFR Fc(s)"). Such chimeric polypeptides are preferred wherein the immunoglobulin portion of each comprises all of the domains except the first domain of the constant region of the heavy chain of human immunoglobulin such as IgG (e.g., IgG1 or IgG3) (column 6, lines 56-65 in particular). Finally, the '820 patent teaches that the combined treatment with TNFbp product(s) and methotrexate has the advantage of achieving the same result with a lower dose or less frequent administration of methotrexate, thereby reducing any toxic effect (column 35, lines 47-67 and column 36, line 1-2 in particular).

As is evidenced in the specification on page 17, lines 4-5, that the claimed TNF- α antagonist is a TNF- α receptor -IgG Fc fusion protein, such as ENBREL (Immunex) is known. ENBREL consists of the extracellular ligand-binding portion of the tumor necrosis factor receptor (TNFR) linked to the Fc portion of human IgG1. The Fc component of ENBREL contains the CH2 domain, the CH3 domain and hinge region (page 3, lines 6-9 in particular).

Claim 6 is included, because the reference anti-CD11a antibodies are the same as the claimed anti-CD11a antibodies. Therefore, the anti-CD11a antibody inherent would be a non T-cell depleting antibody.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to formulate the well known ENBREL as is evidenced in the specification on page 17, lines 4-5, or TNF- α receptor -IgG Fc fusion protein in combination with methotrexate taught by the '820 patent with anti-CD11a antibodies taught by the '454 patent in a method of treating rheumatoid arthritis.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because immunoadhesin exploit both the natural affinity of a receptor for its ligand and the effector functions of the immunoglobulin Fc region. Also, the combined treatment with sTNFR Fc(s) and methotrexate has the advantage of achieving the same result with a lower dose or less frequent administration of methotrexate, thereby reducing any toxic effect taught by the '820 patent.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant argues that the '454 patent is not available as prior art under 35 U.S.C. §103(a) as §103(c) applies because both '454 patent and the present application are assigned to Genentech, Inc.

Art Unit: 1644

However, Applicant's statement did not indicate that both the '454 patent and the current application were commonly owned at the time the claimed invention was made. Therefore, the '454 qualifies as art until the records are clear that both the '454 and the current application were commonly owned at the time the claimed invention was made. For a subject matter disqualified as prior art under 35 U.S.C. 103(c) where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

11. No claim allowed


12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad, whose telephone number is (703) 306-3472. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Maher Haddad, Ph.D.
Patent Examiner
Technology Center 1600
February 10, 2003


CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600